IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application Number	:	10/733,064	Confirmation No.:	7824
Applicant	:	Alexander Sulakvelidze, *et al.*		
Filed	:	December 11, 2003		
Title	:	METHOD AND DEVICE FOR SANITATION USING BACTERIOPHAGES		
TC/Art Unit	:	1648		
Examiner	:	Nicole KINSEY		
Docket No.	:	62610.000044		
Customer No.	:	21967		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132

Sir,

I, Gary R. Pasternack, M.D., Ph.D., declare that:

1. I am a named inventor of Application No. 10/733,064 ("the '064 application"). I am also a founder and Vice-President at Intralytix, Inc., the assignee of the '064 application. Since 1998, I have served as Vice-President at Intralytix, Inc. and have been involved in the research and development of bacteriophage-based products and methods.

2. I received a Bachelor of Arts degree from The Johns Hopkins University in 1971 and a M.D. and Ph.D. from The Johns Hopkins University School of Medicine in 1978. I completed my residency and a fellowship at Yale University School of Medicine in pathology. Although my Ph.D. training focused on immunology, I received my degree from the Department of Microbiology at Johns Hopkins University, where I received additional training in microbiology. In addition, as a pathologist, I received additional training in microbiology and infectious disease in the course of my residency.

3. I have been associated with teaching and research in the field of pathology for approximately 24 years. Among other things, I was the founding director of the graduate program in Pathobiology at the Johns Hopkins University School of Medicine. Throughout my work in the field of pathology, I analyzed innumerable tissue samples from a variety of diseased patients. As a result, I am very familiar with determining when a tissue has been infected by bacteria. An infection involves some degree of tissue reaction to the presence of bacteria.

4. Since the founding of Intralytix in 1998, I have been intimately involved in issues of food-borne infectious disease and infectious diseases affecting both poultry and livestock. In the course of establishing a relationship with Perdue Farms that dates back to 1998, I have participated in the design and analysis of experiments aimed at developing bacteriophage-based treatments for these diseases. During this time, I visited Perdue Farms facilities in conjunction with these experiments. I have also visited poultry and livestock facilities in the European Union. Likewise, I have helped plan and analyze experiments for several additional infectious diseases in poultry and livestock in the course of working with a pharmaceutical company that has an established relationship with Intralytix.

5. I have read, and am familiar with, the following documents:

a) the '064 application; and

b) the Non-Final Office Action mailed on November 13, 2007 ("the Office Action") and the references (Merril, Byrd, Berchieri, Taylor, Holzman, Day and Cox) cited therein.

6. I have been asked to comment on what is taught in these references and on the conclusions drawn in the Office Action.

7. A poultry processing system typically comprises of the following: Eggs are laid and collected in an egg collection site. The eggs are then processed (e.g., candling) prior to being placed in an incubator at a hatchery. The eggs are then incubated for approximately 23 days. After the eggs hatch, the freshly-hatched birds are transferred to a chicken house or farm within 12-24 hours. At the chicken house or farm, the

chickens are fed for 49 days. The chickens are then slaughtered, processed, washed and further processed. The processed chickens are then transported to the point of sale.

8. At the time of hatch, a bird's digestive tract is essentially sterile (i.e., does not contain bacteria). *See* Discussion of Byrd in ¶ 13 below. This absence of bacteria may be contrasted with an infection, where bacteria are present.

9. "Therapy" relates to the treatment of an infection, whereas "prophylaxis" relates to the treatment for the prevention of disease. Bacteriophages have been used therapeutically for many years to treat a variety of bacterial infections and diseases. *See* Specification of the '064 application, page 7, line 20 to page 9, line 3.

10. Claims 43-45 and 88-89 of the '064 application relate to methods of applying at least one bacteriophage to at least one freshly-hatched bird before transferring said at least one freshly-hatched bird to a chicken house. Claims 94-95 relate to similar methods and additionally include steps of providing drinking water or food to said bird in said chicken house, wherein said drinking water or food comprises at least one bacteriophage. As described above (¶ 8), such freshly-hatched birds would not be infected.

11. The Merril reference relates to therapy for animals having bacterial infections. *See, e.g.*, Merril at abstract; col. 3, lines 45-49 and 56-67; col. 8, lines 4-5 and 14-18; col. 9, lines 39-41 and 54-56. In particular, Merril states:

> The administration of an anti-HDS phage that has been developed by serial passage or by genetic engineering will enable the animal recipient to efficaciously fight an infection with the corresponding bacterial pathogen. The phage therapy of this invention will therefore be useful either as an adjunct to standard anti-infective therapies, or as a stand-alone therapy. Col. 3, lines 61-67.
>
> While it is contemplated that the present invention can be used to treat any bacterial infection in an animal, it is particularly contemplated that the methods described herein will be very useful as a therapy (adjunctive or stand-alone) in infections caused by drug-resistant bacteria. Col. 8, lines 14-18.

Merril also teaches that the "phage are administered until successful elimination of the pathogenic bacteria is achieved." Col. 11, lines 1-3.

12. Merril teaches using his modified bacteriophages to evade the host immune system in animals infected with the respective pathogenic bacteria. I would not be led by Merrill to apply bacteriophages to freshly-hatch birds — birds that sterile (i.e., do not contain bacteria) are therefore not infected by pathogenic bacteria. Freshly-hatched birds do not require "therapy."

13. The Byrd reference is concerned with characterizing the spread of *Salmonella* in chickens. Byrd teaches that a newly-hatched bird's digestive tract is essentially sterile. *See* Byrd, page 76, first column, first full paragraph. Byrd also teaches that "[d]ay-of-hatch chicks that had not been inoculated [with *Salmonella*] and had no contact with birds given *Salmonella* ... were negative for *Salmonella* after 17 days." *See* Byrd, page 76, under "Experimental Procedures." Byrd does not indicate that day-old chicks are infected, nor does Byrd teach that day-old chicks are candidates for treatment. At best, Byrd suggests controlling *Salmonella* by reducing levels in the breeder flocks (i.e., at the egg collection site) and then maintaining low levels throughout the processing systems. *See* Byrd, page 79, second column. Moreover, Byrd does not discuss any method for treating *Salmonella* infection and in particular does not mention the use of bacteriophages.

14. Berchieri relates to treatment of infection. Berchieri inoculates chickens with *Salmonella* to establish a *Salmonella* infection and then applies bacteriophage to treat the *Salmonella* infection. This is contrary to the claimed invention which relates to applying bacteriophages to birds that are not infected by pathogenic bacteria (i.e., to "freshly-hatched" birds).

15. I agree with the Office Action's assertion on page 5 that Berchieri teaches infection of chicks. To the extent that the Office Action suggests, however, that Berchieri teaches that chicks may be naturally infected with *Salmonella* within a few hours of hatching, I disagree. Berchieri merely observes that if chicks are infected, then morbidity and mortality can result. As discussed in the preceding paragraph, it is

Berchieri himself that infects the chicks with *Salmonella* as part of his experimental protocol.

16. Taylor relates to the introduction of bacteriophage into infected eggs to combat infection and increase hatch percentage. In particular, Taylor's method "provides a method for increasing the percentage hatch of fowl eggs" by "introduc[ing] a small quantity of a selected bacteriophage, which is known to destroy the particular objectionable bacteria ... through the shell of the whole egg and then incubate the treated egg." Col. 1, lines 15-16 and 52-56; *see also* Examples 1-3. Taylor does not, however, not teach a method of applying at least one bacteriophage to at least one freshly-hatched bird.

17. Holzman is a generic reference that suggests applying bacteriophage for a variety reasons including at least therapy. Holzman identifies that some bacteria have developed resistance to antibiotics. *See* page 12. Holzman suggests that bacteriophage therapy may be used to combat these drug-resistant bacteria. *See* pages 12 and 41. Holzman does not disclose any specific method and/or steps for carrying out a method of using bacteriophages. In particular, Holzman does not teach a method of applying bacteriophage to a bird at a particular stage (e.g., after hatching and before transferring the bird to a chicken house or spraying bacteriophage onto the surface of eggs, wherein said spraying occurs in a hatchery).

18. I agree with the Office Action's assertion on page 2 that Day discloses "treating ruminant livestock with bacteriophage" and "does not teach treating poultry livestock with bacteriophage." In particular, Day discloses treatment of ruminant flora (column 4, lines 26-42), and specifically indicates infection of the rumen by *clostridia* followed by destruction of the infecting *clostridia* using bacteriophage. *See* col. 4, lines 38-40). In view of both Merril and Day, I might consider using Merril's genetically modified bacteriophage to treat ruminants with clostridial infection in their rumen. However, the teachings of Day would not have led me to orally administer the bacteriophage of Merril to freshly-hatched chickens which are not infected.

19. Claims 90-93 of the '064 application relate to methods of spraying at least one bacteriophage onto the surface of eggs, wherein said spraying occurs in a hatchery.

20. I agree with the Office Action's assertion on page 10 that Taylor "does not teach spraying the phage onto the surface of the egg." As discussed above (¶ 16), Taylor is directed to the introduction of bacteriophage into infected eggs to increase hatch percentage. Taylor's method *depends* on the introduction of bacteriophage *into* the egg. Taylor's method therefore would not lead me to perform a method of spraying bacteriophage onto the surface of eggs where the spray does not penetrate the egg shell.

21. Taylor uses a syringe or pressure differential to introduce the bacteriophage into the egg. *See, e.g.*, col. 1, lines 58-63; *see also* Examples 1-3. The eggs are then incubated for 22 days. *See* Examples 1-3. Taylor's method is therefore directed to treating eggs immediately (or shortly) after being laid.

22. The claimed invention is directed to spraying bacteriophages at the hatchery, not where eggs are collected immediately (or shortly) after being laid, i.e., the egg collection site. The invention relates to spraying bacteriophages before hatch so as to minimize bacterial contamination as the chicks hatch. If one were to apply bacteriophages to the surface of an egg immediately (or shortly) after lay (i.e., not shortly before hatch), like Taylor, then the egg will be predisposed to recontamination prior to hatch and bacterial contamination will not be minimized at hatch. Therefore, even if Taylor's method incidentally kills bacteria on the surface of an egg, it would be not be useful in performing the claimed methods.

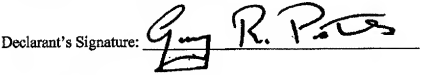
23. Cox relates to the use of chemical sanitizers. Cox teaches that "a freshly laid egg is wet and warm, susceptible to rapid penetration by microorganism." Cox, page 234, first column. Because a freshly-laid egg is susceptible to contamination, Cox recommends that "the appropriate chemical should be applied as soon as economically possible after lay." Cox, page 235, first column. Cox therefore would lead me to spray a sanitizer to an egg immediately (or shortly) after being laid. Cox would not lead me to spray a sanitizer at the hatchery so as to minimize bacterial contamination as the chicks hatch.

24. Both Cox and Taylor are directed to treating eggs shortly after they are laid, to affect the egg during incubation. Byrd, like Cox and Taylor, suggests that the control of *Salmonella* must begin with the breeder flocks (i.e., where the eggs are laid). Such methods are not suited to methods aimed at reducing contamination just before or just after hatch. Therefore, Taylor, Cox and Byrd are not pertinent to the present invention.

I declare further that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on: May 13, 2008

Declarant's Signature: 

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